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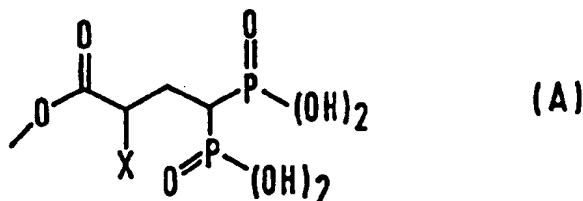
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(54) Title: STEROID BISPHOSPHONATES



(57) Abstract

Bisphosphonate derivatives of hydroxy steroids which are bone resorption inhibitors or bone formation stimulators, the derivatives having at least one group A in place of a hydroxy group on the steroid molecule, where A is a group of formula (A) where X is: (i) St-O-CO- where St is the residue of the hydroxy steroid given by removal of an OH group; (ii) R¹-O-CO- where R¹ is an alkyl, alkenyl, cycloalkyl, aralkyl or aryl group, any of which may optionally be substituted; or (iii) a hydrogen atom, and the salts and solvates of these compounds. The steroid is typically 17β-oestradiol, oestrone, testosterone, norethindrone, androsterone, norethandrolone or nandrolone. The derivatives can be used in the treatment of bone disorders such as osteoporosis.

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STERIOD BISPHOSPHONATES

- 5 This invention concerns steroid derivatives and in particular bisphosphonate derivatives of hydroxy steroids for use in the prevention or treatment of osteoporosis and related bone disorders.
- 10 Hydroxy steroids such as oestradiol and testosterone have been proposed for use in the treatment of osteoporosis, either by inhibition of bone resorption or stimulation of bone formation, and bisphosphonates such as disodium etidronate and clodronate are also known as
- 15 bone resorption inhibitors. Certain bisphosphonate derivatives of steroids have also recently been proposed for these purposes in EP-A-0496520 and EP-A-0548884. In the compounds of EP-A-0496520 the steroidal group is
- linked to the bisphosphonate group by a carbamate or
- 20 carbonate group, and EP-A-0548884 describes steroid bisphosphate ethers.

We have now found a new group of bisphosphonate derivatives of such steroids which are linked by a

25 carboxyl group and, by virtue of the affinity of the bisphosphonate groups for bone, have the potential to target the active steroid selectively on bone and then release the active material in situ by hydrolysis. The compounds of the invention are thus of interest in the

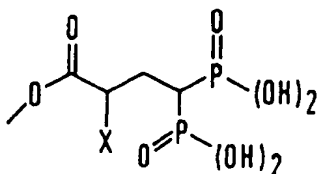
30 prevention or treatment of osteoporosis and other bone disorders such as Paget's disease, bone metastases and malignant hypercalcaemia.

The compounds of the invention are derivatives of

35 hydroxy steroids which are themselves bone resorption inhibitors or bone formation stimulators and thus useful in the prevention or treatment of osteoporosis, the

derivatives having at least one group A in place of a hydroxy group on the steroid molecule, where A is a group of the formula

5



(A)

where X is:

10

(i) St-O-CO- where St is the residue of the hydroxy steroid given by removal of an OH group,

15

(ii) R¹-O-CO- where R¹ is an alkyl, alkenyl, cycloalkyl, aralkyl or aryl group, any of which may optionally be substituted, or

(iii) a hydrogen atom. The invention also includes salts and solvates of these compounds.

20

The compounds of the invention may thus have the formula St-A where St and A are as defined above. Particular groups of compounds of interest are those of the formulae:

25

- (1) (St-O-CO)₂CHCH₂CH(PO(OH)₂)₂
- (2) (St-O-CO)(R¹-O-CO)CHCH₂CH(PO(OH)₂)₂
- (3) (St-O-CO)CH₂CH₂CH(PO(OH)₂)₂

30

Where the steroid contains more than one hydroxy group, only one is usually replaced by a group A, but the invention includes derivatives of such compounds in which two or more hydroxy groups are replaced by A groups.

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The structural variety of the compounds of the invention allows their hydrolysis properties to be modulated as required. For example, most known steroid-

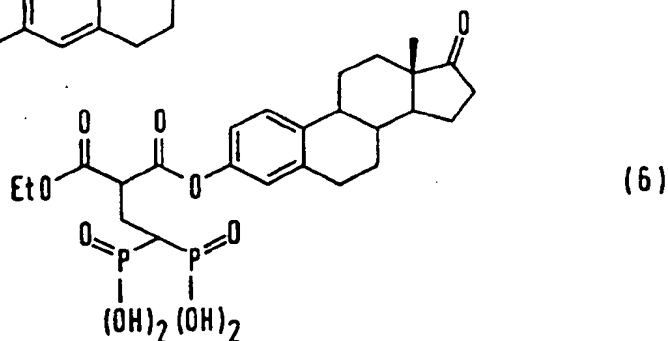
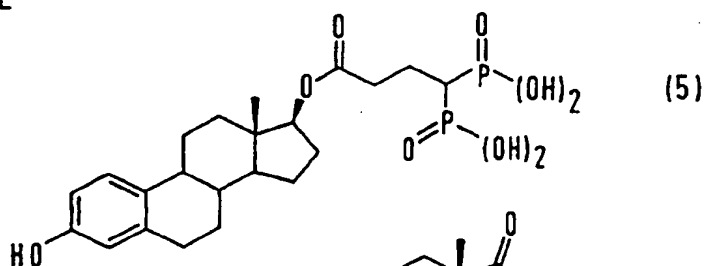
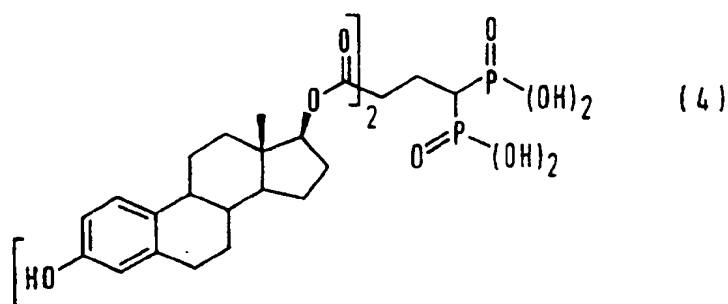
bisphosphonate conjugates, particularly oestradiol-biphosphonates, hydrolyse very rapidly whereas slower hydrolysis and hence slower release of the steroid is often desirable. Compounds of formula (1) above such as the compound (4) below which contains two steroid units are resistant to hydrolysis and thus advantageous when a slower rate of steroid release is required. On the other hand, compounds containing only one steroid unit are less resistant to hydrolysis and thus more suitable when rapid steroid release is required. The compounds of formula (1) also enable two different steroid units to be included in the same molecule, and this allows steroids of different activities to be delivered at the same time.

The parent hydroxy steroid may be an oestrogen, androgen, anabolic steroid, glucocorticoid or progestagen which inhibits bone resorption or stimulates bone formation, such as for example 17β -oestradiol, oestrone, testosterone, norethindrone, androsterone, norethandrolone and nandrolone. These compounds generally have a hydroxy group at the 3- or 17- position or both, and further examples of hydroxy steroids which may be used are listed in EP-A 0496520.

In the group X, R^1 may be a C_{1-6} alkyl (e.g. methyl, ethyl, isopropyl or t-butyl), C_{2-6} alkenyl (e.g. allyl), C_{3-8} cycloalkyl (e.g. cyclopentyl or cyclohexyl), phenyl (C_{1-6})alkyl or a mono- or bicyclic aryl group (e.g. phenyl or naphthyl). The alkyl and alkenyl groups may for example be substituted by one or more halogen atoms (e.g. chlorine) and the cycloalkyl groups by one or more C_{1-4} alkyl groups or halogen atoms (e.g. chlorine). The aryl groups may be substituted by one or more hydroxy groups, as in naphthol.

The compounds of the invention are capable of forming salts with bases and examples of such salts are alkali metal (e.g. sodium) and alkaline earth metal (e.g. calcium) salts. Some compounds of the invention exist in enantiomeric forms and all such forms are included.

Particular compounds of importance have the following formulae:



The compounds of the invention are useful in the prevention or treatment of osteoporosis and the other bone disorders referred to above in man and animals and they may be formulated for these purposes as pharmaceutical compositions together with one or more pharmaceutically acceptable carriers, excipients or

- 5 -

diluents. The active ingredient in these compositions may for example be a compound (4), (5) or (6) shown above.

- 5 The pharmaceutical compositions of the invention may be in a form suitable for oral, buccal, parenteral or topical administration.

10 For oral administration, compositions may be in the form of, for example, tablets, lozenges or capsules containing pharmaceutically acceptable excipients such as binding agents, fillers, lubricants, disintegrants or wetting agents. The tablets may also be coated by known methods. Liquid preparations for oral administration
15 may be in the form of solutions, syrups or suspensions and may contain pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives.

- 20 The compositions may also be formulated for use by injection and may be presented in unit dose form, e.g. in ampoules. The compositions for injection may be in the form of suspensions, solutions or emulsions, in oily or aqueous vehicles, and may contain formulatory agents
25 such as suspending, stabilising, solubilising and/or dispersing agents.

The compositions may also be in a form suitable for topical administration, e.g. transdermal patches,
30 ointments, creams and lotions.

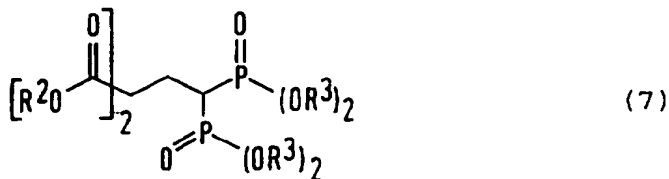
The compounds of the invention may be administered in combination with other pharmaceutically active ingredients.

35

The total daily dosages of compounds of the invention employed in medicine will suitably be in the range

0.001-10.0 mg/kg bodyweight and these may be given in divided doses, i.e. 1-4 times per day.

Compounds of the invention in which X is a group (i),
for example compounds of formula (1) above, may be prepared by transesterification of the carboxylic ester group of a compound of formula (7)



15 (where R² and R³ are C₁₋₆ alkyl groups, e.g. ethyl, and may be the same or different) with the hydroxy steroid (StOH), to give a phosphonate ester (8) of the formula (St-O-CO)₂CHCH₂CH(PO(OR₃)₂)₂, followed by hydrolysis of the phosphonate ester group to give the desired
20 bisphosphonic acid.

The transesterification of (7) may be effected in the presence of a base catalyst such as DMAP (dimethylaminopyridine), for example in a hydrocarbon
25 solvent at any suitable temperature up to reflux.

When the parent hydroxy steroid contains a further hydroxy group which is to remain in the final product, this should be protected during the transesterification
30 reaction (for example as a benzyl ether) and the protecting group subsequently removed.

The hydrolysis of the ester (8) may be carried out with a tri (C₁₋₆ alkyl) silyl halide such as trimethylsilyl
35 bromide, for example in a halogenated hydrocarbon solvent.

- 7 -

The bisphosphonates (7) may be prepared by first reacting a methylene bisphosphonate (9)

5



10

with paraformaldehyde (e.g. in the presence of a base catalyst such as diethylamine) followed by elimination of methanol to give a methyldiene compound (10)

15

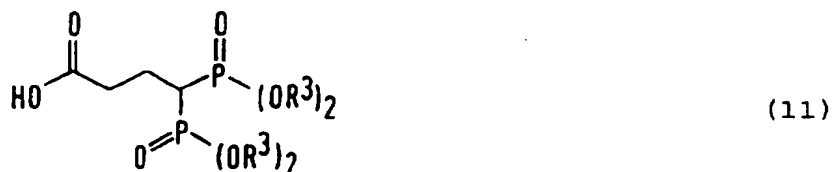


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which is then reacted with a dialkylmalonate (in which the alkyl group is R^2 as defined above) in the presence of a base catalyst (e.g. sodium ethoxide).

25

Compounds in which X is a group (iii), for example compounds of formula (3) above may be prepared by esterification of the hydroxy steroid (StOH) with the acid (11)



30

The reaction may be carried out in the presence of a base and an activating agent such as EDCI (N-(3-ethyldimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride). The phosphonate ester groups may then be removed by hydrolysis as described above to give the

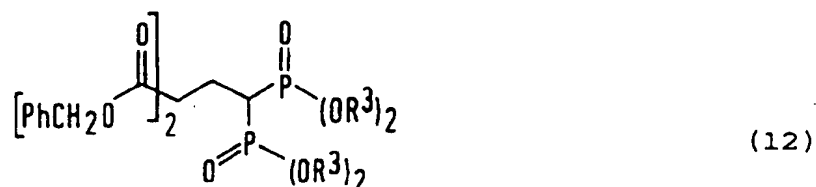
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required bisphosphonic acid.

Again, when the hydroxy steroid contains a further hydroxy group which is to be retained, it should be protected during the reaction and subsequently removed.

- 5 The acids (11) can be prepared from a methylenedio compound (10) above by addition of a dibenzyl malonate, in the presence of a non-nucleophilic base catalyst, to give the ester (12)

10



- 15 followed by hydrogenolysis (e.g. over palladium on carbon) and subsequent decarboxylation (e.g. by heating).

- 20 Compounds in which X is a group (ii), for example compounds of formula (2) above may be prepared from a malonate (13) of the hydroxy steroid



- 25 by reaction with a methylenedio compound (10) in the presence of a non-nucleophilic base to give the addition product (14)

30



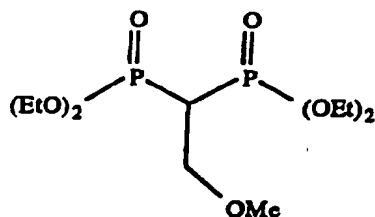
- 35 followed by removal of the phosphonate ester group by hydrolysis as described above to give the desired bisphosphonic acid.

The following examples illustrate the invention.

EXAMPLE 1

Synthesis of Tetraethyl ethylidene bisphosphonate (16)

(i)

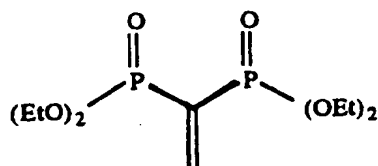


(15)

Tetraethyl methylene bisphosphonate (47.4 g, 0.165 mol, 1.0equiv.), paraformaldehyde (24.75 g, 0.825 mol, 5.0equiv.), diethylamine (17.1 ml, 12.1 g, 0.165 mol, 1.0equiv.) were added to methanol (470 ml). The reaction mixture was heated at 60 °C until the mixture became a colourless solution (30 minutes), and stirred for a further 15 hours at room temperature. The mixture was concentrated under reduced pressure, and toluene (150 ml) added. The solvent was removed under reduced pressure. The addition of toluene followed by a second concentrating process aided the removal of methanol from the crude viscous intermediate product 15. δ_H (CDCl₃) 1.29 (12H, t, J = 8, P-OCH₂CH₃), 2.67 (1H, tt, J_{H-P} = 24, J_{H-H} = 5, P₂CHCH₂OCH₃), 3.32 (3H, s, -OCH₃), 3.86 (2H, td, J_{H-P} = 17, J_{H-H} = 5, P₂CHCH₂OCH₃), and 4.15 (8H, m, P-OCH₂CH₃).

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(ii)

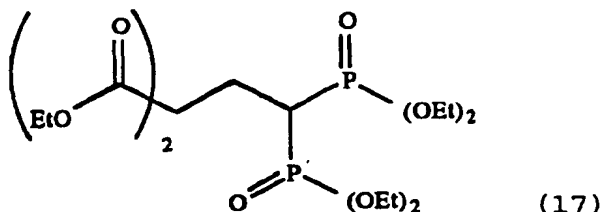


(16)

Toluene-p-sulfonic acid (0.15 g, catalytic) was added to a solution of crude tetraethyl (2-methoxy) ethylidene bisphosphonate 15 in toluene (250 ml). The reaction mixture was heated overnight, under reflux conditions, after this period of time elimination had gone to completion. The reaction mixture was washed with water (3 x 100 ml), and the solvent removed under reduced pressure to yield 16 as an oil (43.16 g, 88% for 2 steps); ν_{\max} 3020, 2960, 1485, 1452, 1402, 1270 (b), and 1050 (b); δ_{H} (CDCl₃) 1.30 (12H, t, $J = 8.0$, P-OCH₂CH₃), 4.0 - 4.2 (8H, m, P-OCH₂CH₃), and 6.94 (2H, dd, trans $J_{\text{P-H}} = 40.0$, cis $J_{\text{P-H}} = 36.4$, P₂C=CH₂); δ_{C} (CDCl₃) 16.15 (4C, t, $J = 3.4$, P-OCH₂CH₃), 63.08 (4C, d, $J = 3.4$, P-OCH₂CH₃), 132.58 (1C, t, $J = 127$, P-C-P) and 149.11 (1C, s, -P₂C=CH₂); m.s. (CI) m/z 301 (M⁺+H).

EXAMPLE 2

Synthesis of Hexa ethyl-[3,3-bis(oxycarbonyl)]propylidene bis[phosphonate] (17)



(17)

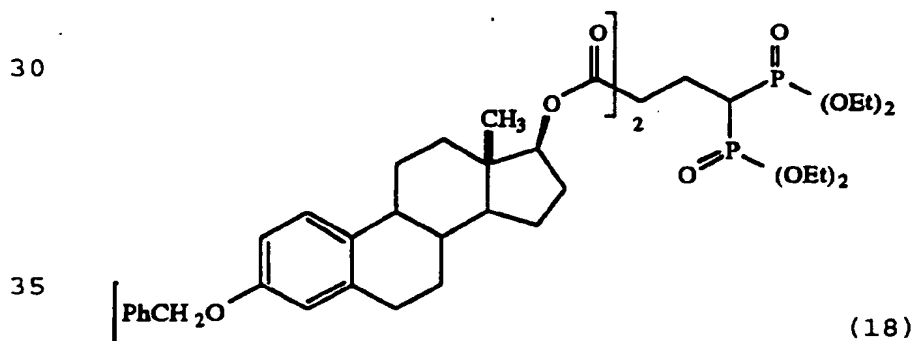
Sodium (0.23 g, 10 mmol, 0.1 equiv.) was dissolved in ethanol (100ml) and stirred at 0°C under a nitrogen atmosphere. The mixture was allowed to warm to ambient temperature until all the sodium had dissolved. The

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sodium ethoxide solution prepared *in situ* was transferred via a cannula to a solution of 16 (30.0 g, 100 mmol, 1.0 equiv.) and diethyl malonate (15.20 ml, 16.02 g, 100mmol, 1.0equiv.) in ethanol (50ml). The reaction mixture was stirred under an atmosphere of nitrogen at ambient temperature for 30 minutes. The reaction mixture was washed with aqueous HCl 1M (3 x 100ml) and extracted into CH₂Cl₂ (200ml). The organic fraction was collected and dried with anhydrous MgSO₄, the solvent was removed under reduced pressure final traces of solvent were removed under high vacuum. The desired product 17 was isolated as an oil in excellent yield (43.8g / 95.1%). (Found: C 43.97 H 7.55, C₁₇H₃₄O₁₀P₂ requires: C 44.35 H 7.44); ν_{\max} 3010, 1749, 1732, 1270 (b), and 1045 (b) cm⁻¹; δ_{H} (CDCl₃) 1.28 (6H, t, J = 7.16, CO₂CH₂CH₃), 1.35 (12H, t, J = 7.12, PO₂CH₂CH₃), 2.33 - 2.75 (3H, m), 3.97 (1H, t, J = 7.68, -CH(CO₂Et)₂), and 4.12 - 4.27 (12H, m); δ_{C} (CDCl₃) 14.48 (2C, s, -CO₂CH₂CH₃), 16.71 (4C, d, J_{CP} = PO₂CH₂CH₃), -25.29 (1C, t, J_{CP} = 5, -CHCH₂CH-), 34.71 (1C, t, J_{CP} = 132, P-C-P), 50.51 (1C, t, J_{CP} = 8, -CH₂CH(CO₂Et)₂), 61.97 (2C, s, -CO₂CH₂CH₃), 63.22 (4C, t, J_{CP} = , PO₂CH₂CH₃), and 169.31 (2C, s, -CO₂Et); δ_{P} CDCl₃) 22.33; m/z (CI) 461 (M⁺+H).

25 EXAMPLE 3

Synthesis of Tetraethyl {3,3-bis-[3-benzyloxy-estra-1,3,5-triene-17 β -yloxycarbonyl]propylidene} bis[phosphonate] (18)



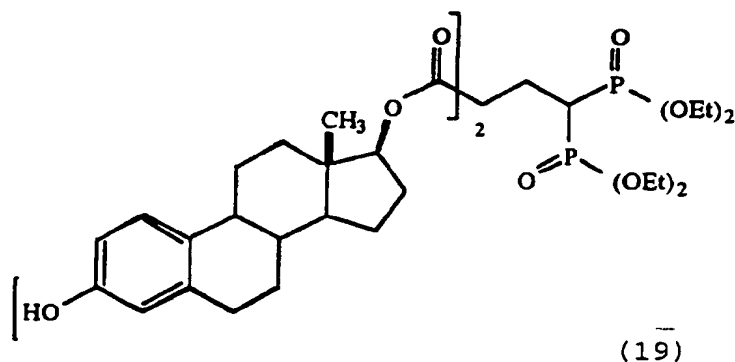
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4-(*N,N*-dimethylamino)pyridine (0.013 g, 0.11 mmol, 0.1 equiv.) and 3-benzyl-17 β -oestradiol (0.861 g, 2.39 mmol, 2.2 equiv.) were added to a solution of 17 (0.50 g, 1.09 mmol, 1.0 equiv.) in toluene (10 ml). The reaction mixture was heated under reflux for 11 days under an atmosphere of nitrogen. The solvent was removed under reduced pressure and the crude product absorbed onto silica gel. The product was purified by silica gel flash column chromatography, the eluent used was 1-3% methanol in CH₂Cl₂, the desired product was obtained as a viscous oil (0.80 g, 67%); ν_{\max} 3017, 2936, 1724, 1605, 1498, 1203 (b), and 929; δ_{H} (CDCl₃) 0.84 (3H, s, 18'-CH₃), 0.88 (3H, s, 18'-CH₃), 1.23 - 1.97 (21H, m), 1.35 (12H, t, *J* = 7), 2.15 - 2.36 (13H, m), 4.72 - 4.81 (2H, m, 17'H), 5.05 (4H, s, -OCH₂Ph), 6.74 (2H, s, 4'H), 6.80 (d, 2H, *J* = 9, 2'H), 7.23 (d, 2H, *J* = 9, 1'H), and 7.30 - 7.47 (m, 10H); δ_{C} (CDCl₃) 13.09, 13.20, 17.43, 17.51, 24.35, 26.19, 27.24, 28.29, 28.53, 30.82, 35.51 (t, *J*_{CP} = 132, PCP), 37.95, 44.15, 44.31, 44.84, 50.80, 51.38 (t, *J*_{CP} = 7.3, -CHCH₂CH(CO₂R)₂), 63.83 (t, *J*_{CP} = 6.9, -CH₂CH(CO₂R)₂), 71.00, 85.02 (d, *J*_{CP} = 10.4, PO₂CH₂CH₃), 113.39, 115.92, 127.42, 128.49, 128.89, 129.59, 133.73, 138.39, 138.95, 157.84, and 169.96 (d, *J*_{CP} = 3.5, -CH(CO₂R)₂); δ_{P} (CDCl₃) 20.4; *m/z* (+ve ion FAB) 1094 (M⁺+H, 100).

25

EXAMPLE 4

Synthesis of Tetraethyl {3,3-bis[estra-1,3,5-triene-3-hydroxy-17 β -yloxycarbonyl]propylidene} bis[phosphonate] (19)

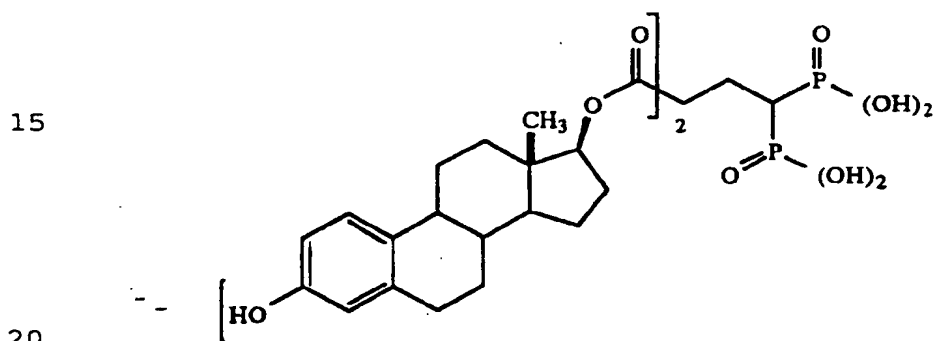


To a solution containing 18 (692 mg, 0.633 mmol, 1.0 equiv.) in tetrahydrofuran/methanol 1:1 (10 ml) was added 10% Pd/C (140 mg). The reaction mixture was shaken under an atmosphere of hydrogen (1 bar) for 6 hours. The reaction mixture was filtered, taken up into CH₂Cl₂, and washed with brine. The organic layer was collected and dried with anhydrous MgSO₄, and the solvent removed under reduced pressure. The product was purified further by silica gel flash column chromatography, eluted with 3 - 5% methanol in CH₂Cl₂. The solvent was once again removed and the product was produced as a foam under high vacuum (557mg, 96.4%); (Found: C, 64.68; H, 7.76. C₄₉H₇₀O₁₂P₂ requires: C, 64.46; H, 7.73); δ_H (CDCl₃) 0.775 (3H, s, 18'-CH₃), 0.781 (3H, s, 18'-CH₃), 1.15 - 1.87 (21H, m), 1.34 (12H, t, J = 6.8, P-OCH₂CH₃), 2.09 - 2.33 (6H, m), 2.49 (2H, heptet, J = 7.6, P₂CHCH₂CH(CO₂R)₂), 2.66 (1H, tt, J_{P-H} = 24, J_{H-H} = 7.2 P₂CHCH₂CH(CO₂R)₂), 2.81 (4H, m), 4.05 (1H, t, J = 7.6, P₂CHCH₂CH(CO₂R)₂), 4.16 - 4.24 (8H, m, P-OCH₂CH₃) 4.71 (2H, q, 9.2, 17'H), 6.58 (2H, s, 4'H), 6.66 (2H, d, J = 8, 2'H), and 7.08 (2H, d, J = 8.8, 1'H); δ_C (CDCl₃) 11.93 (1C, 18'C), 12.03 (1C, 18'C), 16.29 (4C, d, J = 5, P-OCH₂CH₃), 23.22 (2C), 24.95 (1C, b-P₂CHCH₂CH-), 26.16 (2C), 27.18 (1C), 27.37 (1C), 29.53 (2C), 34.17 (1C, t, J = 134, P-C-P), 36.81 (2C), 38.56

(2C), 42.98 (2C), 43.17 (1C), 43.68 (1C), 49.64 (2C),
 50.23 (1C, t, J = 9, P₂CHCH₂CH(CO₂R)₂) 63.06 (4C, t, J =
 7, P-OCH₂CH₂), 83.95 (1C, 17'C), 84.09 (1C, 17'C), 112.77
 (2C), 115.31 (2C), 126.22 (2C), 131.48 (2C), 131.53
 5 (2C), 137.79 (2C), 154.23 (2C), and 168.84 (2C, -CO₂R);
 δ_p (CDCl₃) 20.7(s); m/z (+ve ion FAB) 913 (M⁺+H, 76), 159
 (100).

EXAMPLE 5

10 Synthesis of 3,3-Bis-(estra-1,3,5-trien-3-hydroxy-17 β -
 yloxycarbonyl) propylidene bis(phosphonic acid) (20)



(20)

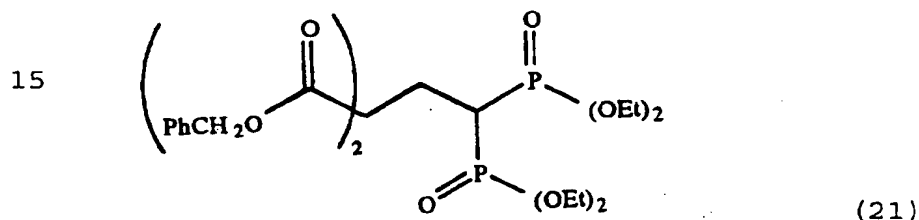
To a solution of 19 (250 mg, 0.275 mmol, 1.0 equiv.) in
 CCl₄ / CHCl₃ 1:1 (3 ml) was added trimethylsilyl bromide
 25 (1.24 ml, 1.47 g, 9.62 mmol, 35 equiv.) and the mixture
 stirred for 24 hours under a nitrogen atmosphere. Water
 (5 ml) was added and an off white solid formed. The
 precipitate was filtered and washed with cold water and
 CH₂Cl₂. The product was dried under high vacuum and
 30 obtained as an off white powder (206 mg, 94%) which
 decomposes at 180 °C; δ_H (CD₃OD) 0.85 (3H, s, 18'-CH₃),
 0.86 (3H, s, 18'-CH₃), 1.20 - 2.05 (21H, m), 2.10 - 2.30
 (5H, m), 2.38 - 2.50 (3H, m), 2.70 - 2.81 (4H, m), 4.08
 (1H, t, J = 7, -CH₂CH(CO₂H)₂), 4.72 (2H, t, J = 8,
 35 17'H), 6.47 (2H, d, J = 2, 4'H), 6.53 (2H, dd, J = 9, J
 = 2, 2'H), and 7.05 (2H, d, J = 9, 1'H); δ_C (CD₃OD) 12.64
 (1C, 18'C), 12.71 (1C, 18'C), 24.22 (2C), 26.37 (1C, b,

- 15 -

-P₂CHCH₂CH-), 27.44 (2C), 28.45 (2C), 28.52 (2C), 30.63 (2C), 36.79 (1C, t, J = 127, P-C-P), 38.16 (2C,b), 40.18 (2C), 44.28 (1C, 13'C), 44.40 (1C, 13'C), 45.10 (2C), 50.94 (2C), 52.04 (1C, b, -CH(CO₂R)₂), 85.26 (1C, 17'C), 85.34 (1C, 17'C), 113.79 (2C), 116.08 (2C), 127.21 (2C), 132.36 (2C), 138.73 (2C), 155.94 (2C, 3'C), and 170.49 (2C, -CO₂R); δ_p (CD₃OD) 22.6; m/z (-ve ion FAB) 799 (M⁻-H, 100).

10 EXAMPLE 6

Synthesis of Tetraethyl [3,3 bis(benzyloxycarbonyl)]propylidene bis[phosphonate] (21)



20 Tetraethyl ethylidene bisphosphonate 16 (1.00 g, 3.33 mmol, 1.0 equiv.), and dibenzyl malonate (0.83 ml, 0.946 g, 3.33 mmol, 1.0 equiv.) were dissolved in tetrahydrofuran (15 ml). Lithium bis(trimethylsilyl) amide solution in tetrahydrofuran (1M), (0.33 ml, 0.33 mmol, 0.1 equiv.), was added to the reaction mixture and stirred for one hour at room temperature. Saturated aqueous ammonium chloride (50 ml) was added to the reaction mixture and the product extracted into CH₂Cl₂ (100ml). The organic layer was collected and dried with anhydrous MgSO₄, the solvent was removed under reduced pressure. The crude product was absorbed onto silica gel and purified by silica gel flash column chromatography, eluted with 2-3% methanol/ CH₂Cl₂. The product was isolated as a colourless oil (1.12 g, 58% yield);

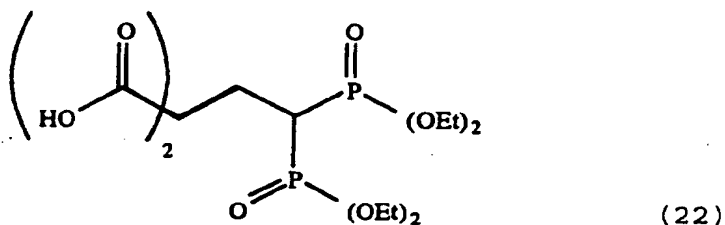
35 δ_H (CDCl₃) 1.30 (6H, t, J = 7.1, -OCH₂CH₃), 1.31 (6H, t, J = 7.1, -OCH₂CH₃), 2.37 - 2.74 (3H, m), 4.07 - 4.24 (9H, m), 5.14 (4H, s, -OCH₂Ph), and 7.24 - 7.35 (10H, m);

- 16 -

$\delta_{\text{C}}(\text{CDCl}_3)$ 16.10 (2C, $-\text{OCH}_2\text{CH}_3$), 16.24 (2C, $-\text{OH}_2\text{CH}_3$), 24.81 (1C, m, $-\text{CH}_2\text{CHP}_2$) 34.11 (1C, t, $J_{\text{C-P}} = 132.1$, P-C-P), 49.93 (1C, t, $J_{\text{C-P}} = 7.8$, $-\text{C}(\text{O})\text{CHRC}(\text{O})$), 62.66 (4C, m, $-\text{OCH}_2\text{CH}_3$), 67.11 (2C, $-\text{OCH}_2\text{Ph}$), 128.03 (4C, ortho C), 128.22 (2C, para C), 128.40 (4C, meta C), 135.12 (2C, 1' on Ph) and 168.41 (2C, $-\text{OC}(\text{O})\text{CH}$); $\delta_{\text{P}}(\text{CDCl}_3)$ 32.19; m/z (+ve ion FAB) ($\text{M}^+ + \text{H}$) 585 (36), 369 (7), and 91 (100); HRMS ($\text{M}^+ + \text{H}$) (Found: 585.20184 $\text{C}_{27}\text{H}_{34}\text{P}_2\text{O}_{10}$ requires: 585.20185).

EXAMPLE 7

Synthesis of Tetraethyl 3,3bis(phosphono)-propylidene bis(carboxylic acid) (22)



21 (0.698 g, 1.19 mmol), was dissolved in tetrahydrofuran (10 ml), and palladium activated charcoal (0.10 g, cat.) added. The reaction mixture was stirred under an atmosphere of hydrogen, overnight, at room temperature. The reaction mixture was filtered and washed with saturated aqueous ammonium chloride (50 ml). The product was extracted into CH_2Cl_2 and dried with anhydrous MgSO_4 , the solvent was removed under reduced pressure, and the product dried under high vacuum as a white solid, (0.42 g, 88% yield); $\delta_{\text{H}}(\text{MeOD})$ 1.35 (12H, t, $J = 6.6$, $-\text{P-O-CH}_2\text{CH}_3$), 1.74 (2H, heptet, $J = 7.7$, $\text{P}_2\text{CHCH}_2\text{CH-}$), 2.08 (1H, tt, $J_{\text{P-H}} = 23.1$, $J = 6.6$, P-CHRP), 3.18 (1H, t, $J = 6.6$, $-\text{CH}_2\text{CH}(\text{CO}_2\text{H})_2$), 3.48 - 3.63 (8H, m, P-O- CH_2CH_3); $\delta_{\text{C}}(\text{MeOD})$ 16.55 (2C, P-O- CH_2CH_3), 16.68 (2C, P-O- CH_2CH_3), 25.95 (1C, t, $J_{\text{P-C}} = 4.0$, $\text{P}_2\text{CHCH}_2\text{CH-}$), 35.01 (1C, t, $J_{\text{P-C}} = 133.4$, P-CHRP), 51.10 (1C, m, $-\text{CH}(\text{CO}_2\text{H})_2$), 64.45 (4C, dd, $J = 9.4$, 6.7, P-O- CH_2CH_3), 171.84 (2C, $-\text{CO}_2\text{H}$); $\delta_{\text{P}}(\text{MeOD})$

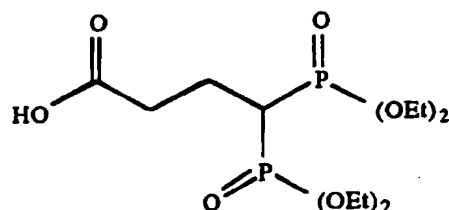
- 17 -

22.8; m/z (+ve ion FAB) ($M^+ + D$) 406 (100), and ($M^+ + H$) 405 (90)

EXAMPLE 8

5 Synthesis of Tetraethyl 4,4-bis(phosphono)-butanoic acid (23)

10



(23)

15 22 (0.200 g, 0.495 mmol), was heated to 130 °C for 3 hours, under a steady stream of nitrogen. The product was obtained as a colourless oil (0.174 g, 99%); δ_H (MeOD) 1.35 (12H, t, $J = 7.7$, $-OCH_2CH_3$), 2.06 - 2.25 (2H, m, $P_2CHCH_2CH_2-$), 2.63 - 2.69 (1H, m, $-CDHCO_2H$), 2.81 (1H, tt, $J_{P-H} = 24.2$, $J = 6.6$, $-PCHP-$), 4.11 - 4.25 (8H, m, $P-O-CH_2CH_3$); δ_C (MeOD) 16.57 (2C, $P-O-CH_2CH_3$), 16.71 (2C, $P-O-CH_2CH_3$), 21.82 - 22.10 (1C, m, $P_2CHCH_2CH_2-$), 32.53 - 33.07 (1C, m, $P_2CHCH_2CH_2CO_2H$), 35.87 (1C, t, $J = 133.4$, $P-CHR-P$), 64.07 - 64.36 (4C, m, $P-O-CH_2CH_3$), and 175.85 (1C, $-CO_2H$); δ_P (MeOD) 24.95; m/z (-ve ion FAB) 361 (100) ($M^- - H$, for di-deuterated product); HRMS (+ve ion FAB) (Found: 363.12997 $C_{12}H_{25}D_2O_8P_2$ requires: 363.13067).

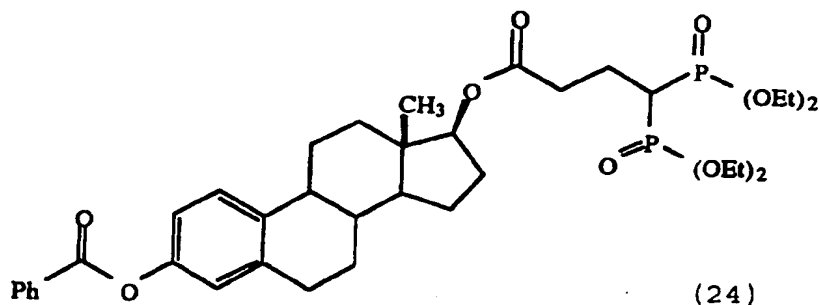
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EXAMPLE 9

30 Synthesis of Tetraethyl {3-[3-benzoyloxy)estra-1,3,5-trien-17 β -yloxycarbonyl] propylidene} bis[phosphonate] (24)

5

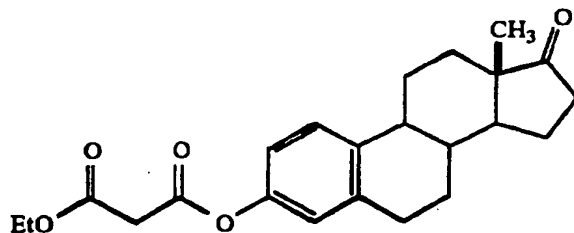


10 23 (0.071 g, 0.20 mmol, 1.0 equiv.), 3-*O*-benzoyl-17 β -
 oestradiol (0.089 g, 0.24 mmol, 1.2 equiv.), and 4-(*N,N*-
 dimethylamino)pyridine (0.005 g, 0.04 mmol, 0.2 equiv.),
 were dissolved in CH₂Cl₂ (5ml), and stirred at 0 °C under
 an atmosphere of nitrogen. EDCI (0.0455 g, 0.24 mmol,
 15 1.2 equiv.), was added to the reaction mixture, and
 allowed to warm slowly to room temperature whilst
 stirring overnight. The reaction mixture was washed with
 water (30 ml), and the product extracted into CH₂Cl₂. The
 organic layer was collected, dried with anhyd. MgSO₄, and
 20 the solvent removed under reduced pressure. The crude
 product was absorbed onto silica gel and purified by
 silica gel flash column chromatography, 1-3% methanol/
 CH₂Cl₂ were used as eluents. The product dried under high
 vacuum and was isolated as colourless oil (0.048 g,
 25 33%); ν_{\max} 3053, 2983, 1729, 1601, 1243, and 1025;
 δ_{H} (CDCl₃) 0.84 (3H, s, 18'-CH₃), 1.25 - 1.93 (11H, m),
 1.35 (12H, t, J = 7.2, P-OCH₂CH₃), 1.12 - 2.74 (7H, m),
 2.87 - 2.92 (2H, m), 4.12 - 4.28 (8H, m, P-OCH₂CH₃), 4.70
 (1H, dd, J = 8.8, 7.1, 17'H), 6.92 - 7.00 (2H, m), 7.33
 30 (1H, d, J = 8.2, 1'H), 7.46 - 7.67 (3H, m), and 8.20
 (2H, dt, J = 8.3, 1.6, ortho H's on Ph); δ_{C} (CDCl₃) 12.06
 (1C, 18'-CH₃), 16.32 (2C, P-OCH₂CH₃), 16.43 (2C, P-
 OCH₂CH₃), 21.04 (1C, m, P₂CHCH₂CH₂-), 23.25 (1C), 26.03
 (1C), 27.00 (1C), 27.59 (1C), 29.50 (1C), 35.68 (1C, t,
 35 J = 132.1, P₂-CHR), 36.86 (1C), 38.18 (1C), 38.35 (1C),
 42.87 (1C), 43.98 (1C), 49.80 (1C), 62.61 (4C, t, J =
 6.7, P-OCH₂CH₃), 82.74 (1C, 17'C), 118.67 (1C), 121.58

(1C), 126.43 (1C), 128.49 (2C), 129.70 (1C), 130.10 (2C), 133.45 (1C), 137.84 (1C), 138.19 (1C), 148.68 (1C), and 172.72 (2C); $\delta_p(\text{CDCl}_3)$ 23.2; m/z (+ve ion FAB) 721 (M^+H , for product containing 2D), 720 (M^+H , for product containing 1D), and 719 (M^+H). The benzyl and ethyl groups can be removed by the methods of Examples 4 and 5.

EXAMPLE 10

Synthesis of Ethyl 17-oxoestra-1,3,5,-trien-3-yl propionate (25)



(25)

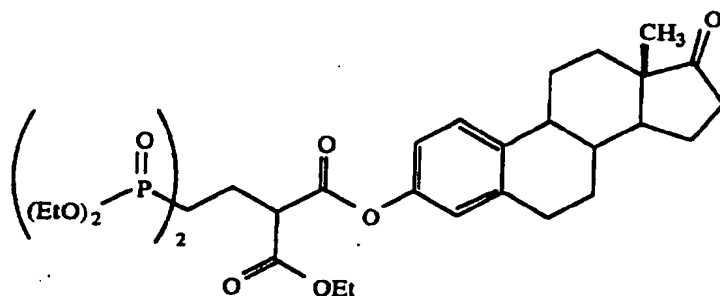
Oestrone (0.54 g, 2.0 mmol, 1.0 equiv.), triethylamine (0.56 ml, 0.405 g, 4.0 mmol, 2.0 equiv.), were dissolved in tetrahydrofuran (15 ml) and stirred at 0 °C under an atmosphere of nitrogen. Ethyl malonyl chloride (0.76 ml, 0.903 g, 6.0 mmol, 3.0 equiv.) was added slowly to the reaction mixture, which was allowed to warm to room temperature and stirred overnight. The reaction mixture was washed with water (2 x 50 ml), and the product extracted into CH₂Cl₂, and dried with anh. MgSO₄. The solvent was removed under reduced pressure, the crude product absorbed onto silica gel and purified by silica gel flash column chromatography, eluted with 0.5% methanol/CH₂Cl₂. The product was isolated as a colourless oil (0.144 g, 19% yield); $\delta_H(\text{CDCl}_3)$ 0.90 (3H, s, 18'-CH₃), 1.32 (3H, t, J = 7.1, -OCH₂CH₃), 1.36 - 1.75 (6H, m), 1.88 - 2.59 (7H, m), 2.91 (2H, dd, J = 8.3, 3.8), 3.59 (2H, s, malonate H), 4.26 (2H, q, 7.1, -OCH₂CH₃), 6.86 - 6.91 (2H, m), and 7.29 (1H, d, J = 8.2, 1'H); $\delta_C(\text{CDCl}_3)$

- 20 -

13.65, 13.95, 21.41, 25.60, 26.13, 29.21, 31.39, 35.68, 37.83, 41.47, 43.98, 47.75, 50.26, 61.58, 118.35, 121.18, 126.30, 137.65, 138.00, 148.22 (3'C), 165.25 (-CO₂Et), 166.09 (-CO₂Ph), and 214.04 (17'C); m/z (+ve ion FAB) 385 (38) (M⁺+H), 115 (100).

EXAMPLE 11

Synthesis of Tetraethyl [4-ethoxy-4-oxo-3-(17-oxoestra-1,3,5-trienyloxycarbonyl)-butylidene] bis[phosphonate] (26)



(26)

25 (0.112 g, 0.291 mmol, 1.0 equiv.), and 16 (0.087 g, 0.291 mmol, 1.0 equiv.), were dissolved in tetrahydrofuran and stirred at room temperature under an atmosphere of nitrogen. A solution of lithium bis(trimethylsilyl)amide (1M) in tetrahydrofuran (0.03 ml, 0.03 mmol, 0.1 equiv.) was added to the reaction mixture and stirred for 3 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride, and the product extracted into CH₂Cl₂. The organic layer was collected and dried with anh. MgSO₄. The solvent was removed under reduced pressure and the crude product adsorbed onto silica gel. The product was purified by silica gel flash column chromatography, 0.5 - 3% methanol/CH₂Cl₂ as eluent. The product was isolated and dried under high vacuum to give a colourless oil (0.060 g, 30%); δ_H (CDCl₃) 0.91 (3H, s, 18'-CH₃), 1.27 - 1.72 (8H, m), 1.37 (12H, t, J = 7.2, P-O-CH₂CH₃), 1.90 - 2.95 (13H, m), 4.13 - 4.33 (11H, m), 6.82 - 6.90 (2H, m), and

- 21 -

7.30 (1H, d, $J = 8.8$, 1'H); δ_c (CDCl₃) 13.76 (1C, 18'C),
 14.06 (1C, -CO₂CH₂CH₃), 16.24 (2C, -PO₂CH₂CH₃), 16.35 (2C,
 -PO₂CH₂CH₃), 21.53 (1C, P₂CHCH₂CH-), 24.96 (1C, m), 25.70
 (1C), 26.24 (1C), 29.32 (1C), 31.50 (1C), 34.28 (1C, t,
 5 $J = 132.1$, P-C-P), 35.76 (1C), 37.97 (1C), 44.11 (1C),
 17.86 (1C), 49.93 - 50.23 (1C, m, -C(O)CHRC(O)-), 50.42
 (1C), 61.77 (1C, -CO₂CH₂CH₃), 62.66 - 62.98 (4C, m, P-O-
 CH₂CH₃), 118.35 (1C), 121.18 (1C), 126.36 (1C), 137.70
 (1C), 138.08 (1C), 148.38 (1C), 167.73 (1C), 168.54 (1C),
 10 and 214.15; δ_p (CDCl₃) 22.34, and 22.44; m/z (+ve ion FAB)
 685 (57) ($M^+ + H$), 239 (100); HRMS (Found: 685.29124
 C₃₃H₅₀O₁₁P₂ requires: 685.29066).

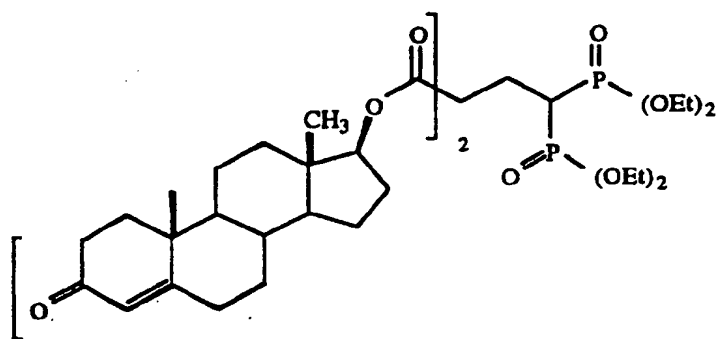
(26) may be converted to the corresponding bisphosphonic
 15 acid by the method of Example 5.

EXAMPLE 12

Synthesis of Tetraethyl {3,3-bis[androst-4-en-3-one-17 β -
 20 yloxyacarbonyl]propylidene} bis[phosphonate] (27)

20

25



(27)

30 Testosterone (0.500 g, 1.73 mmol, 2.2 equiv.), 17 (0.363
 g, 0.788 mmol, 1.0 equiv.), and 4-(N,N-
 dimethylamino)pyridine, were dissolved in toluene (7 ml)
 and heated under reflux, under an atmosphere of
 nitrogen. After 10 days reflux, more testosterone (0.250
 35 g, 0.86 mmol, 1.1 equiv.) was added to the reaction
 mixture, and heated under reflux conditions for another
 6 days. The reaction was stopped and washed with

saturated aqueous ammonium chloride. The product was extracted into CH_2Cl_2 , and dried with anh. MgSO_4 . The solvent was removed under reduced pressure, and the crude product absorbed onto silica gel. The product was

5 purified by silica gel flash column chromatography, 3% methanol/ CH_2Cl_2 was used as the eluent. The product was isolated as a foam under a high vacuum (0.61 g, 82% based on 3); δ_{H} (CDCl_3), 0.76 (3H, s, 18'- CH_3), 0.78 (3H, s, 18'- CH_3), 0.80 - 1.80 (20H, m), 1.12 (6H, s, 19'- CH_3),

10 1.28 (12H, t, $J = 7.2$), 1.94 - 1.98 (2H, m), 2.05 - 2.57 (13H, m), 3.94 (1H, t, $J = 7.6$, malonate H), 4.58 (2H, q, $J = 8$, 17'H), and 5.66 (2H, s, 4'H); δ_{C} (CDCl_3), 11.91 (1C), 12.02 (1C), 16.31 (2C), 16.42 (2C), 17.39 (2C), 20.49 (2C), 23.45 (2C), 24.82 - 25.02 (1C, m), 27.31

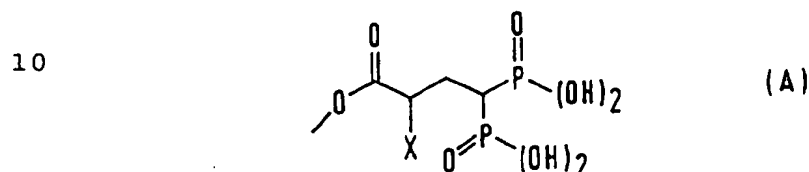
15 (2C), 31.43 (2C), 32.67 (2C), 33.88 (2C), 34.34 (1C, t, $J = 133.4$), 35.34 (2C), 35.69 (2C), 36.53 (2C), 38.57 (2C), 42.56 - 42.72 (2C, m), 50.17 (2C), 53.61 (2C), 61.51 (1C), 62.61 - 62.92 (4C, m), 83.50 (1C), 83.64 (1C), 123.97 (2C), 168.80 (1C), 168.88 (1C), 170.77

20 (2C), and 199.37 (2C); δ_{P} (CDCl_3), 22.98; m/z (+ve ion FAB) ($\text{M}^+ + \text{H}$) 946 (14), 703 (87), and 461 (100).

(27) may be converted to the corresponding bisphosphonic acid by the method of Example 5.

CLAIMS

1. Bisphosphonate derivatives of hydroxy steroids
which are bone resorption inhibitors or bone formation
5 stimulators, the derivatives having at least one group A
in place of a hydroxy group on the steroid molecule,
where A is a group of the formula



where X is:

- 15 (i) St-O-CO- where St is the residue of the hydroxy steroid given by removal of an OH group;
- 20 (ii) R¹-O-CO- where R¹ is an alkyl, alkenyl, cycloalkyl, aralkyl or aryl group, any of which may optionally be substituted; or

(iii) a hydrogen atom,

25 and the salts and solvates of these compounds.

2. Compounds according to claim 1 of the formula (1)



30

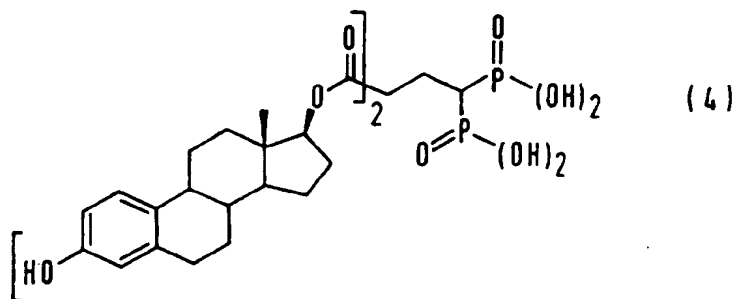
3. Compounds according to claim 1 or claim 2 wherein the steroid is an oestrogen, androgen, anabolic steroid, glucocorticoid or progestagen.

- 35 4. Compounds according to claim 1 or claim 2 wherein the steroid is 17 β -oestradiol, oestrone, testosterone, norethindrone, androsterone, norethandrolone or

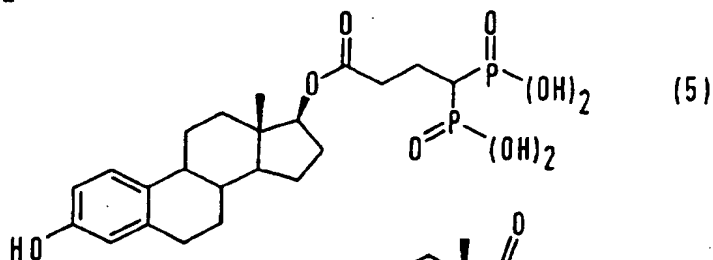
nandrolone.

5. A compound according to claim 1, said compound being:

5

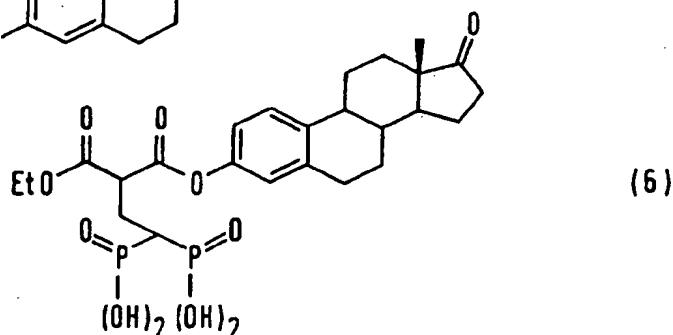


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or

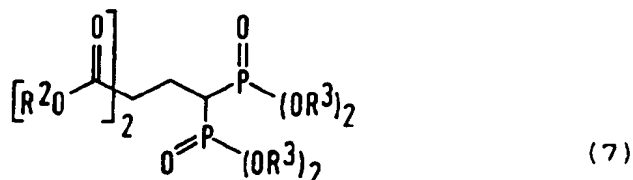


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25 6. A pharmaceutical composition containing one or more compounds according to any preceding claim and one or more pharmaceutically acceptable carriers, excipients or diluents.

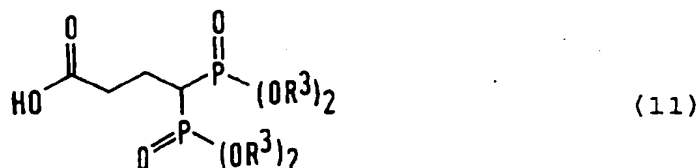
30 7. A process for the preparation of a compound according to claim 1 which comprises:

(A) in the preparation of a compound in which X is a group (i), transesterifying the carboxylic ester groups
35 of a compound of formula (7)



5
 10 (where R^2 and R^3 are C_{1-6} alkyl groups and may be the same or different) with the hydroxy steroid (StOH), to give a phosphonate ester (8) of the formula $(\text{St}-\text{O}-\text{CO})_2\text{CHCH}_2\text{CH}(\text{PO}(\text{OR}^3)_2)_2$, followed by removal of the phosphonate ester groups by hydrolysis;

15 (B) in the preparation of a compound in which X is a group (iii), esterifying the hydroxy steroid (StOH) with the acid (11)

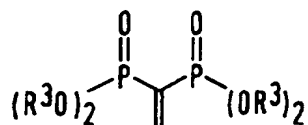


20 followed by removal of the phosphonate ester groups by hydrolysis; or

25 (C) in the preparation of a compound in which X is a group (ii), reacting a malonate (13) of the hydroxy steroid

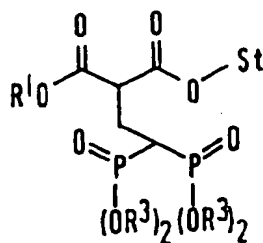


30 with a methyldene compound (10)



35 to give the addition product (14)

5



(14)

10 followed by removal of the phosphonate ester groups by
hydrolysis.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/01748

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J51/00 A61K31/565

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. GUERVENOU ET AL: PHOSPHORUS, SULFUR AND SILICON AND THE RELATED ELEMENTS, vol. 88, no. 1-4, 1995, pages 1-13, XP002040871	1,3,6,7
Y	see the whole document	1-7
X	FR 2 683 527 A (BRETAGNE OCCIDENTALE UNIVERSIT) 14 May 1993	1,3,6,7
Y	see the whole document, in particular example 3, NOTE: formulae of examples 2 and 3 as drawn are incorrect, see text of both examples	1-7
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

17 September 1997

Date of mailing of the international search report

03. 10. 97

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International Application No
PC1/GB 97/01748

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